CPC COMBINATION PRODUCT COALITION

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Divisions of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2005N-0098
Food and Drug Administration/Drug Information Association
Cross Labeling; Public Meeting; Combination Products and
Mutually Conforming Labeling

Dear Sir or Madam:

Thank you very much for organizing the meeting in collaboration with the Drug Information Association on May 10. We found the May 10 meeting extremely helpful and very well done. The interactive discussion helped us to crystallize our thinking, and we hope it helped the agency as well.

The Combination Product Coalition ("CPC") is a group of about 15 companies that span the drug, medical device and biological product industries. The Coalition's members include both large and small companies that represent a wide variety of specific therapeutic areas. We think our diversity is a unique strength of our group because it forces us to look at combination product issues from nearly every perspective reflected in the industry today. While that certainly makes policy development more of a challenge, it ultimately means that the positions we develop should have broader support. It may be interesting to point out that at least three of our members presented at the May 10 meeting, and the different perspectives were evident from those presentations.

After the meeting, we took the materials presented and went through them as a group to consider and formulate answers to the basic questions posed. In response to those questions, we will offer a general comment first, then some specific observations.

General Comment

Our general comment is that we believe most of the agency's questions would be addressed by adopting a clear understanding of what is and is not a combination product. When the definition of "combination product" is properly framed, it becomes clear that cooperation is required to create a combination product under 21 C.F.R. § 3.2(e)(3). And further, a review of the rest of the Federal Food, Drug and Cosmetic Act demonstrates that the agency may not compel or otherwise force a company to cooperate with another in the development and approval of a combination product. At the same time, numerous product combinations exist that are very close to constituting "combination products," but technically are not "combination products." We call these "almost combination products." In these cases, we believe the agency has options available to it to approve products even where formal cooperation between the parties is absent.

This is a very important point, so please allow us to restate it in perhaps another way. FDA has asked what its regulatory authority and responsibilities are for combination products where the manufacturers of the two products are not working together. As explained in more detail below under our specific comments, we suggest that implicit in the definition of combination products at 21 C.F.R. § 3.2(e)(3) is a requirement that cooperation between the two manufacturers is necessary to effectuate the labeling change described in § 3.2(e)(3) and more broadly, to assure safety and effectiveness. So a linchpin to the definition of combination product is an assessment of the need for cooperation. Thus, in answer to FDA's question: if (1) under the definition of a combination product, products may only become combination products if they need cooperation between the two manufacturers to be safe and effective, then (2) where that cooperation is lacking, FDA cannot approve the combination product.

The other implication – and benefit – of this approach is that, if cooperation is not necessary for ensuring safety and effectiveness, then (1) the products do not form a combination product, (2) the combination product statutory and regulatory authorities do not apply, and (3) *FDA has the freedom to approve the products subject to an assessment of the safety and effectiveness issues.* In the observations that follow, we explore what safety and effectiveness issues should be considered for "almost combination products."

Bottom line: We believe the combination product authorities were meant to apply only in those instances where the cooperation of the manufacturers is necessary to ensure the safe and effective use of the products. The only issue left regarding these products, then, is whether FDA can do something to encourage that cooperation, and we address that below.

The specifics of this general comment hopefully will become clear as we discuss our specific observations. In particular, we would like to offer four observations that we think are relevant to the questions with which the agency is struggling.

Specific Comments

1. Scope of Combination Products

a. Current Regulation: Cross-Labeling

For starters, let's discuss what products do and do not qualify as combination products. In this regard, we are only focused on subsection 3 of the definition in 21 C.F.R. § 3.2(e), which provides that:

> A drug, device, or biological product packaged separately and according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

To tease apart its meaning, let's look at four different example scenarios:

(1) General use devices that deliver many drugs. The device label does not cross-reference a specific drug, and no drug label specifically cross-references the device.

(2) A device that is labeled for and specifically designed for the delivery of one specified branded drug, but while the drug labeling does not reference the device, the drug labeling does not conflict with and does not contraindicate the device.

(3) A drug and a device each with labeling that specifically cross-references the other, for example, a pen and associated pre-filled drug cartridges. In this scenario, other manufacturers might later want to seek approval for a new pen or a new cartridge that would be used with the previously-approved companion product.

(4) A drug and a device that are specifically identified in each other's labeling, but where only these products may be used together and there is no substitute for either one.

In these examples, the first two scenarios do not describe a combination product as defined in § 3.2(e)(3) for the simple fact that a combination product requires both of the combined products to specifically cross-reference the other. In the third scenario, when the two products are first approved, they are approved as part of a combination product. But the follow on products are not combination products because they don't require the relabeling of the companion products. In our parlance, we would designate

the first, second, and the follow-on products in the third scenario as "almost combination products." The fourth scenario is clearly a combination product and would remain so.

Thus, as the definition of a combination product is currently written, the development, production and approval of a combination product requires cooperation of the two parties because the only intended use of each of the two articles is to be used with the other. It is therefore hard for us to even imagine how the two articles that comprise a true combination product (as opposed to an "almost combination product") would be developed if the two companies were not cooperating together.

Interesting questions arise with regard to the subsequent approvals described in the third scenario, for example, an approval of a new device for delivering the already-approved drug. Here again, the definition of a combination product parallels the issue of cooperation. Specifically, if: (1) a new device can be developed for administering the drug; (2) the device is slightly different but substantially equivalent in function to the existing device used for delivering the drug; and (3) the new device could be approved without requiring a change to the labeling for the drug, then the second device is no longer part of a combination product because its approval did not require the relabeling of the drug. (Nonetheless, FDA could approve the device using the process that we outline below for almost combination products.) If, on the other hand, the new device is different enough from the old device that its proper use would require new labeling for the drug, the new device would be part of a combination product, and the cooperation of the drug manufacturer would be required.

In summary, then, if mutually conforming labeling is necessary to ensure safety and effectiveness, the products are a combination product and cooperation at least in relabeling is required. If, on the other hand, mutually conforming labeling is not necessary to ensure safety and effectiveness, the products are not combination products. Using our terminology, these are "almost combination products."

b. Current Regulation: References to Products

Another aspect of the current regulation supports the fact that cooperation is necessary to create a combination product. Specifically, in defining the scope and reach of the combination product authorities, we believe FDA has limited the reach of § 3.2(e)(3) ("is intended for use only with an approved individually specified drug, device or biological product") to references to specific, proprietary brands of products. References to generic drug categories, for example, do not create combination products, even though FDA might still choose to impose the requirements we outline below regarding "almost combination products." By the same token, a cross-reference need not be more specific than the brand (such as dosage strength or form) to trigger combination product status. We believe this is the best interpretation of the regulation for two reasons.

First, we believe this interpretation best comports to the plain text reading of the regulation. The phrase "individually specified" conveys an intention on the part of the agency to limit the scope of combination product status to those instances where the

cross-reference is reasonably specific. As a result, we do not think that a reference to a generic category of products was intended to constitute an individually specified product because a class of products is by definition not an individual product. By the same token, we can see no evidence in the drafting of the regulation to suggest that the drug, device or biological product must be identified with regard to its individual strength, for example. Such characteristics do not define the identity of the product but rather communicate its particular form.

Second, we believe this interpretation also best effectuates the public health purposes behind the regulation. This approach captures those instances where products, by virtue of being combined, may create issues related to safety and effectiveness that need to be reviewed with the cooperation of the two companies. It divides the products into two groups depending on whether cooperation is needed, as follows:

- Where FDA permits merely a cross-reference to a generic class of products, FDA apparently has concluded that the issues can be evaluated at a general level for the whole class of cross-referenced products, without cooperation from any particular manufacturer of the class of products.

- On the other hand, if the safety and effectiveness issues among the class of products actually vary from brand to brand, FDA should not permit a general cross-reference and should instead require a cross-reference to a specific brand. That, in turn, suggests to us that FDA needs cooperation between the two companies to assure the safety and effectiveness of the combined product.

In other words, where generic reference to the category of products is sufficient, the device, drug or biological product in whose labeling the cross-reference is found can be evaluated by FDA without the cooperation of any one company that makes the generic product that is being cross-referenced. But when FDA determines that a generic cross-reference is not specific enough to ensure the safety and effectiveness of the combined product, the agency should insist upon a more specific cross-reference that has the effect of triggering combination product status and requires the cooperation of the company whose product is being cross-referenced.

c. Bottom Line Under Current Law

To summarize, we believe the definition is written to work as follows:

(1) Can product B be used safely and effectively with already-approved product A if the labeling for product B only includes a generic reference to the category of products that contains product A?

a) If the answer is yes, the two products together are not combination products, there does not need to be any

cooperation between the two manufacturers, and product B may be approved despite any lack of cooperation.

b) If the answer is no because a specific cross-reference to product A by brand is necessary to assure safety and effectiveness, we must ask a second question:

(2) Do the two companies need to cooperate to ensure that the products can be used together safely and effectively? For example, does company A need to agree to change its labeling to permit the combined use of the products?

a) If the answer is yes, the product is a combination product, and by definition cooperation between the two companies is required for the agency to approve product B.

b) If the answer is no, the two products are not combination products, and there does not need to be cooperation between the two manufacturers, and product B may be approved despite any lack of cooperation.

Bottom line under current law is this: If mutually conforming labeling that specifically cross-references another product by brand is necessary to ensure safety and effectiveness, the products are a combination product and cooperation at least in relabeling is required. And in the absence of that cooperation, FDA can only encourage cooperation on a limited basis, which we describe in more detail below. If, on the other hand, mutually conforming labeling that specifically cross-references by brand the other product is <u>not</u> necessary to ensure safety and effectiveness, the products are not combination products. Using our terminology, these are "almost combination products," which FDA may approve through the process we outline below.

2. Limits on FDA's Authority

FDA's mission and legal authority do not include trying to arrange marriages between drug, device and biologics companies. By choice, America does not have a planned economy. Instead, the marketplace decides whether joint efforts will occur. As the presentations at the meeting described, there are many and differing reasons why a joint effort may not occur, and those reasons may not be transparent even to one of the would-be participants.

Fundamental to this conclusion is that FDA should not apply any pressure on a company to work with another. We have asked a number of companies what they would consider to be pressure, and it appears that companies have a low threshold for feeling pressure by the regulatory agency that governs so much of what they do. We believe that FDA should ask for cooperation from reluctant parties very lightly and frankly in rare circumstances where there is no risk of pressure.

In essence, we draw the line at FDA ordering conforming labeling by the already-approved product's manufacturer. To illustrate our point, we'll again use the example of an approval of a new device for delivering an already-approved drug. If relabeling is necessary to assure safety and effectiveness, we believe that FDA is without legal authority to approve the device in the absence of the willingness of the drug manufacturer to relabel its drug. FDA is also without legal authority to order the drug manufacturer to perform that relabeling. FDA has simply no legal grounds for telling a drug manufacturer that it must relabel its drug in order for the agency to approve a device that would then take advantage of the expanded scope of the drug labeling.

3. FDA Offer Incentives

Even though putting pressure on companies is not appropriate, FDA can offer incentives where it appears that a regulatory issue is the impediment to cooperative progress. Frankly, these will be rare instances because so many of the impediments have nothing to do with regulatory requirements. Moreover, even when regulatory impediments exist, FDA's possible incentives may not be enough. Merely reducing the user fee, for example, may not sufficiently compensate the companies where the overall regulatory impediment is that market size does not justify the costs of developing the needed regulatory data and undertaking the needed regulatory submissions. Similarly, while the incentive of additional exclusivity for the drug may help tilt the scale in favor of proceeding jointly, even that incentive will prove inadequate in many cases. But, we can also imagine a few instances where the incentives would help.

4. Congressional Incentives

Congress could, of course, authorize incentives for this kind of product development that have nothing to do with FDA, such as tax incentives, liability limitations and patent term restoration. We suspect these would focus on strategically needed public health advancements. We don't know whether creating such a system that would be both fair and successful is feasible, but it may be worth examining if policy makers can identify gaps in product development that are having public health consequences. Determining whether those gaps really exist on a macro level would seem to be a logical starting point. Perhaps someone with another HHS agency is in the best position to assess that need.

Proposed Clarification: Guidance Document

While we believe that the existing regulation is written to require cooperation, we also believe that clarifying the meaning of the regulation in a guidance document would benefit both FDA and industry. Below we outline the main points that we believe such a guidance document should address.

1. Cooperation is Required to Create a Combination Product

We believe that a guidance document is appropriate to clarify that cooperation between two companies is necessary to effectuate the labeling change described in § 3.2(e)(3). As explained above, we believe that this interpretation is consistent with the regulation's plain meaning and public policy purposes.

But we must also say that we think the regulation focuses too narrowly on the mutually conforming labeling issue, and fails to explicitly address the broader, related issue of cooperation generally. Instead of merely saying that the need for mutually conforming labeling is the trigger for combination product status, the regulation would have been clearer and better focused if it had made the trigger for combination product status a determination that cooperation between the two companies is necessary to ensure the safe and effective use of the product. Thus, the guidance could clarify that:

> Combination products include a drug, device, or biological product that is packaged separately and according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device or biological product where both are required to achieve the intended use, indication, or effect. Moreover, to be a combination product, it must be clear that upon approval of the proposed product the manufacturer of the approved product would need to cooperate with the manufacturer of the proposed product to assure the safe and effective use of the combined product. Such cooperation could mean, for example, that the manufacturer of the approved product would agree to change the labeling of its product, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

In this regard, to add more definition to what is meant by "cooperation", we might say it means that companies need to agree to do at least one of the following:

(1) Coordinate labeling for their products by mutually cross labeling them,

(2) Work together to communicate on current and future design and modification issues, or

(3) Authorize FDA to make use of data that the agency needs to approve the product B.

Adopting such a definition of cooperation would be broad enough to encompass all that is required to assure the safe and effective use of the combined product.

2. FDA's Role in the Cooperation

We also believe that such a guidance document should address FDA's role in cooperation between two companies. Specifically, clarifying the limits on FDA's authority and specifying examples of situations in which the agency may ask for cooperation from companies would benefit both the agency and industry. In the guidance FDA might also offer examples of incentives it might give for cooperation.

3. FDA Approval Where Cooperation Is Lacking: Approving "Almost Combination Products"

In some instances, FDA has the legal flexibility to approve certain new products that will be used in combination with others, even when cooperation is lacking. These products are the "almost combination products" that do not qualify as combination products under § 3.2(e)(3) because mutually conforming labeling that specifically cross-references by brand the other product is not necessary to ensure safety and effectiveness. (In our four examples on page 3, the "almost combination products" are examples (1), (2), and the follow-on products of (3).) We believe that the guidance document should describe FDA's latitude to approve these "almost combination products" through the process described below.

The cornerstone for determining whether the circumstance allows approval in the absence of cooperation for "almost combination products" would be a risk assessment prepared by the firm seeking the second approval (company B), without the cooperation of the other company (company A). This risk assessment would consider and address such issues as:

(1) The likelihood that product A will be changed in the future.

(2) The consequences of possible changes to product A. Here we would be concerned with any special consequences unique to the combination, as opposed to consequences that would occur regardless of whether product A is used alone or with product B.

(3) The effectiveness of company B's ability to monitor product A for such changes.

(4) The ability of company B to effectively label the combined use without the need to relabel product A (which establishes that combination product status is unnecessary).

(5) The ability of company B to respond to changes to product A in a timely manner.

(6) Any other issues that bear on the ability of company B to assure the safety and effectiveness of the combined product without the cooperation of company A.

This risk assessment would be provided to FDA in the submission seeking clearance or approval for product B. For example, it could be a section of a 510(k) or PMA. In the event of changes to product A, company B would decide what remedial action is necessary based on a risk analysis.

Apart from that risk assessment showing that the risk is manageable, company B would need to be able to satisfy the requirements for clearance or approval of product B, without infringing on company A's ownership of data previously submitted to FDA. Take, for example, a follow-on product where device company B wants approval for a new device that will be used with drug company A's previously-approved drug. Company B could seek a clearance for the device as a drug delivery device that does not cross-reference a specific drug, if that is possible and appropriate, or the device might cross-reference the drug but the drug does not need to cross-reference the device. If the claim of the device company is simply that the device can deliver the drug as safely and effectively as other devices, the claim does not require proving that the drug is safe and effective in any absolute sense. However, perhaps if the device company wants to claim some advantage with regard to safety and effectiveness due to the combination, such a claim might require an examination of the underlying safety and effectiveness of the drug delivered in a conventional way. In this case, FDA would not be entitled to consider data that are the property of company A without company A's permission.

For this pathway to be available at all, product B's labeling must not contradict or require off-label use of product A. For example, if the labeling of a drug specifically calls out a brand of device, then a follow-on device would conflict with the drug labeling. Thus a key element to assuring a follow-on product can be cleared separately is the way the labeling for the initial product is written and approved. Because of this, we believe that FDA should be flexible in approving the way in which combinations are described in the initial labeling so as not to squelch innovation from subsequent manufacturers. The combination may also not call for a dosage or route of administration that is different than or inconsistent with the labeled dosage and route of administration for product A. However, the labeling for product A does not need to include specific directions for the particular use with product B.

Should it need to, under most of the pathways to market, FDA can impose post approval requirements to ensure that company B follows the needed steps called for by the risk analysis. For example, if the product is submitted through a PMA, under 21 C.F.R. § 814.82, FDA can require that the company monitor changes in the companion product and report any changes that require a modification of the device.

Conclusion

Again, thank you for hosting the meeting on this important topic and for soliciting public input. It is quite apparent to us that FDA is very sincerely reaching out for ideas on how to make the combination product program better.

If the agency thinks the ideas in this comment have value, we would be glad to do the work necessary to move this concept further along into a more concrete form. For example, we could develop a draft guidance that we would then submit to the agency for its consideration. We are working this summer to develop two draft guidance documents for the agency to consider on modifications to already approved product, and to the selection criteria for deciding which regulatory requirements apply to combination products that are post-approval. We could turn to the cross labeling issue this fall and similarly developed a draft guidance for it, if that would be timely. When we develop these guidance documents, we reach out to any and all parties who are willing to sit down and work with us on these projects. Please let us know if the agency would be interested in seeing such a proposal.

Very truly yours,

Bradley Merrill Thompson